



# **Armed Forces College of Medicine AFCM**



# **Mixed agonist- antagonist & opioid toxicity**

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# INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

1. Explain the advantages of mixed agonist-antagonist analgesics
2. Identify therapeutic uses of opioid antagonists
3. discuss the Manifestations, Cause Of Death and treatment of Acute morphine poisoning
4. discuss the Manifestations, Cause Of Death and treatment of Chronic morphine poisoning (addiction)

# Main points:

- Mixed-agonist antagonist narcotic analgesics cause weak respiratory depression compared to morphine
- Naloxone & Naltrexone are opioid antagonists
- Management of acute morphine poisoning differ from the management of chronic poisoning.

# ***Mixed Agonist ( $\kappa$ ) - Antagonist ( $\mu$ ) Narcotic Analgesics***

- 1- IF NO Morphine addiction → Kappa ( $\kappa$ )-Agonist → Analgesic.
- 2- IF Morphine Addiction →  $\mu$ -Antagonist → Withdrawal manifestations.
- 3- Weak □ R.C. (Partial agonist) → Low ceiling effect.  
□ Dose of these drugs → More Analgesia But No More □ R.C.
  - Mild dependence → Mild withdrawal manifestations.

	$\mu$	$\kappa$	$\sigma$
- <b>Pentazocine</b>	Antagonist	Agonist	<b>Agonist</b>
- <b>Butorphanol</b>	Antagonist	Agonist	-
- <b>Nalbuphine</b>	Antagonist	Agonist	<b>Agonist</b>
- <b>Buprenorphine</b>	<b>P.A.</b>	<b>Antagonist</b>	-

# Quiz

- A 63 years old woman is complaining of cancer breast & metastasis to the bone, the physician prescribed butorphanol to relieve her pain. Butorphanol is:
    - a. An antagonist on opioid receptors
    - b. A partial agonist on opioid receptors
    - c. A mixed agonist antagonist opioid analgesic
    - d. A non-steroidal anti-inflammatory drug
    - e. A non-opioid analgesic
- The answer is C: A mixed agonist antagonist opioid analgesic

# Narcotic Antagonists

- Opiate receptor antagonist:- Block all actions (Therapeutic & Toxic) of Morphine & other Opioids.



# 1- Naloxone

- Pure antagonist. More selective on  $\mu$ -receptors.
- **Therapeutic uses:**
  - a- Acute Morphine poisoning → 0.4 mg I.V. to be repeated due to Short  $t_{1/2}$  = 1 hour.
  - b- Opioid-induced Neonatal asphyxia → Mother (IM) or Neonate (Intraumbilical).
  - c- Diagnosis of Opioid addiction → S.C. → Withdrawal manifestations e.g. Mydriasis

## 2- Naltrexone

- Similar to Naloxone → Pure antagonist, more selective on  $\mu$ -receptors.
- But → Stronger, Longer & Effective orally.
  - - Uses:
    - a- Orally to maintain the Opiate-free state of treated addict.
    - b- Acute Morphine poisoning.

# Acute Morphine Poisoning:

- a- Manifestations: Coma + PPP + Hypoventilation, Hypoxia, Hypotension & Hypothermia.
- b- Cause Of Death → Respiratory Failure.
- c- Treatment:
  - Artificial respiration. No pure O<sub>2</sub> → Apnea.
  - Stomach wash in Every case even after parenteral poisoning.  
Use K-Permanganate + Charcoal + MgSO<sub>4</sub>.
  - Specific Morphine Antagonists e.g. **Naloxone** (0.4 mg I.V.).

# Quiz

- Symptoms of acute morphine toxicity include:
  - a. Coma, pinpoint pupils and depressed respiration
  - b. Hyperthermia
  - c. Abdominal cramps, diarrhea and miosis.
  - d. Hypertension & cardiac arrhythmias
  - e. Dry mouth and mydriasis

The answer is A: Acute poisoning does not cause neither hyperthermia nor hypertension. It cause pinpoint pupils.

# Chronic Poisoning → Addiction:

- a- Tolerance → Psychic Dependence → Physical Dependence.
- b- Due to □ Endogenous Endorphins & Enkephalins.
- c- The addict → PPP, constipation, Psychosis (drug seeking habit) & moral deterioration.
- d- Sudden stop of Morphine or use of Morphine antagonist → **Withdrawal or Abstinence** → Psychic craving for Morphine, Anxiety, yawning, lacrimation, rhinorrhea then reversal to all actions of morphine → Excitation, severe pain, fever, mydriasis, hyperventilation, hypertension, tachycardia, diarrhea & urination. All these symptoms disappear on taking morphine.

- e- Management of Morphine addiction:
  - Hospitalization + Psychotherapy.
  - Gradual withdrawal of Morphine till the stabilizing dose.
  - Gradual substitution with Methadone → Similar to Morphine But Less withdrawal manifestations
  - Gradual withdrawal of Methadone.
  - Alpha 2 agonists: e.g:
    - Clonidine → Control many withdrawal symptoms.
    - Lofexidine (better than clonidine)
  - Acupuncture → □ Release of endogenous endorphins & enkephalins.
  - Oral Naltrexone →  $\mu$ -Antagonist → # Euphoria → Dysphoria.

# Quiz

- A morphine addict arrived to the hospital and presented by pinpoint pupil and psychosis and complaining of severe constipation. What is the best management to this case?
  - a. Substitution of morphine by methadone then withdrawal methadone + Clonidine + Naltrexone
  - b. Substitution of morphine by nalbuphine then withdrawal of nalbuphine + Clonidine + Naltrexone
  - c. Substitution of morphine by methadone then withdrawal of methadone + Serotonin + Naltrexone
  - d. Substitution of morphine by nalbuphine then withdrawal of Nalbuphine + Meperidine + Naltrexone
  - e. Substitution of morphine by methadone then withdrawal of methadone + Clonidine + Meperidine

The answer is A: Substitution of morphine by methadone then withdrawal methadone + Clonidine + Naltrexone

# Lecture Quiz



**1- Which of the following drugs is used in treatment of morphine or heroin addiction:**

Butorphanol

Methadone

Alfentanil

Sufentanil

Dextropropoxyphene

**2- Which of the following is a pure opioid antagonist?**

Methadone

Nalbuphine

Naloxone

Buprenorphine

Pentazocine



# To Summarize

- Importance of mixed agonist antagonist narcotic analgesics
- Opioid antagonists
- Acute & chronic morphine poisoning.

## SUGGESTED TEXTBOOKS



1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7<sup>th</sup> edition.). Philadelphia: Wolters Kluwer
2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14<sup>th</sup> edition) New York: McGraw-Hill Medical.